PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCB72471WO00	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/GB2004/002678	International filing date *(day/month/year)* 22.06.2004	Priority date *(day/month/year)* 26.06.2003
International Patent Classification (IPC) or national classification and IPC C07K5/08		
Applicant PEPHARM R&D LIMITED et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.11.2004	01.06.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Meacock, S Telephone No. +49 89 2399-7603

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002678

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-46	as originally filed
Claims, Numbers	
1-8	received on 04.05.2005 with letter of 04.05.2005
Drawings, Sheets	
1/5-5/5	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002678

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 4-7

because:

☒ the said international application, or the said claims Nos. 4-7 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-8
	No:	Claims	1, 2
Inventive step (IS)	Yes:	Claims	3-8
	No:	Claims	1, 2
Industrial applicability (IA)	Yes:	Claims	1-3, 8
	No:	Claims	(4-7, opinion reserved)

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

1. The following documents are referred to in this communication:

D1: WO 03/006492 A
D3: FURKA A et al (2000), J. Comb. Chem., vol. 2, no. 3, pages 220-223

2. Novelty (Article 33(2) PCT)

2.1 The subject-matter of Claims 1 and 2 does not appear to be novel in view of the teaching of the cited prior art.

2.2 D3 discloses a synthesis method for oligomers, and exemplifies the method with a 125-member tripeptide library using Chiron crowns as solid support units and a simple manual device for sorting.

Present Claim 1 relates to an "isolated or purified peptide". The applicant has argued that D3 merely discloses a pool of a highly complex nature of which the tripeptide tyrosyl-seryl-valine (YSV) is among its components. Thus, the applicant considers that D3 does not disclose the "isolated or purified" feature of the claimed peptide.

D3 is concerned with the production of combinatorial libraries, and provides an example in which "crowns" attached to a string are used as solid support units. Each crown is therefore a synthesis site, onto which the tripeptides are built. Each tripeptide is attached to a crown, and twenty-five such crowns are on any one string. D3 describes how the crowns were sorted in order to ensure formation of all possible structural combinations during the synthesis; sorting involves transferral of the crowns into slots of a tray and removal of the string. The implication of this method, in particular the sorting aspect, is that it teaches that the tripeptides are always distinct entities. In fact, it can be said that whilst the tripeptides are on the crowns, they **cannot** form a mixture, since they are not free. Thus, the YSV tripeptide of D3 is not merely one component of a complex pool; it is a distinct entity which is purified away from the other peptides during the sorting.

2.3 Even if the view were taken that the presence of the Chiron crown renders the attached

tripeptide unpure, the applicant's attention is brought to the fact that the disclosure of D3 would still be relevant to **inventive step**; the purification of an entity is common practice for a person skilled in the art. D3 describes the removal of the Chiron crown from five of the synthesised peptides, by cleavage (page 223).

In conclusion, the applicant's argument is not accepted, and D3 is considered to disclose an isolated or purified tripeptide with the sequence YSV (Table 3 position 20, string 4). This is novelty destroying for claims directed to the polypeptide per se (Claims 1 and 2).

3. **Inventive step (Article 33(3) PCT)**

Claims 3-8 are directed to applications of the peptide consisting of the tripeptide YSV. The closest prior art is considered to be D1. D1 discloses the tripeptides YSL and YSF. These two tripeptides display similar activities to the presently-claimed YSV; modulation of the immune response, growth of different types of cancer etc.

Starting from D1, the problem to be solved may be formulated as provision of a further tripeptide which is useful in treatment of different types of cancer and as a nutritional supplement.

The solution to this problem as provided by the present claims, is to substitute the C-terminal residue of YSL for a valine residue.

The skilled person, aware of the tripeptide YSL described in D1, and aware of the teaching in D1 whereby for peptides with non-polar or hydrophobic side chains it may be possible to substitute one side group for another without reducing the biological activity (see p. 56, lines 36-40), might consider at least conservative substitutions of the only non-polar or hydrophonic side chain residue in this peptide; the C-terminal leucine residue. However, the context of this passage is not one that relates to tripeptides specifically, it teaches modifications to peptides generally. Thus, the range of possible modifications may be viewed as being a reasonably sized group.

The applicant has argued that the tripeptide displays a surprising effect in that it has relatively high potency (compared with the tripepetides YSL and YSF) in inhibiting human hepatoma

xenograft growth in mice, and inhibits human leukemia cells (whereas YSL does not).

The claimed peptide, YSV, is a conservative substitution which does not reduce the biological activity, apparently producing instead additional desirable effects. Thus, the selection of valine is considered to represent a selection of a tripeptide sequence with a surprising technical effect.

In conclusion, an inventive step over D1 may be acknowledged for the subject-matter of Claims 3-8.

4. Industrial applicability

Claims 4-7 are directed to a method of treatment of the human or animal body.

For the assessment of Claims 9-12 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims (Rule 39 PCT).

Claims

1. An isolated or purified peptide consisting of the tripeptide L-Tyrosyl-L-Seryl-L-Valine.

2. The peptide of Claim 1 wherein said peptide has an activity selected from the group consisting of modulation of an immune response, stimulation of T lymphocyte transformation, modulation of a cell proliferative disorder, modulation of the growth of a cancer, modulation of the growth of a liver cancer, modulation of the growth of leukemia cells, modulation of the growth of a cervical cancer, modulation of the growth of a lung cancer and the modulation of the growth of a melanoma.

3. A pharmaceutical composition comprising a polypeptide consisting of the tripeptide L-Tyrosyl-L-Seryl-L-Valine.

4 A method of reducing the condition of a human disease comprising administering a pharmaceutically effective dose of a polypeptide consisting of the tripeptide L-Tyrosyl-L-Seryl-L-Valine to a human, wherein said human disease is selected from the group consisting of a condition that can be reduced by stimulating T lymphocyte transformation and a cell proliferative disorder.

5. The method of Claim 4, wherein said cell proliferative disorder is cancer.

6. The method of Claim 5, wherein said cancer is selected from the group consisting of liver cancer, leukemia, lung cancer, melanoma and cervical cancer.

7. The method according to Claim 4, wherein said disease may be treated by modulation of immune system.

8. Use of a peptide consisting of the tripeptide L-Tyrosyl-L-Seryl-L-Valine as a nutritional supplement.